Efficient and chemoselective alkylation of amines/amino acids using alcohols as alkylating reagents under mild conditions†

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We report a mild and environmentally benign method for the synthesis of tertiary amines using alcohols as the alkylating reagents. Not only secondary amines such as piperazines but also amino acids and amino alcohols can be *N*-alkylated selectively. For *N*,*O*-benzyl protected amino alcohols, both *N*,*O*-de-benzylation and *N*-methylation were achieved in one-pot.

Amines are an important class of compounds in both chemistry and medicinal chemistry.[1] Many *N*-methyl and *N*,*N*-dimethyl amino acid residues are found in bioactive natural products (*vide infra*).[2] The classical methods for the synthesis of amines, such as alkylation of amines with organo-halides[3] and reductive alkylation of amines with carbonyl compounds,[4,5] disobey to the principles of green chemistry,[6,7] because in both methods, the starting materials, alkyl halides and carbonyl compounds, need to be prepared from alcohols. In addition, both their preparation and transformation to amines involve environmentally hazardous reagents.

The development of environmentally benign methods[6] featuring amongst others, atom-economy,[8] step-economy,[9] and the use of readily available reagents and chemicals[7] is highly desirable, yet challenging. In this context, direct conversion of C–H bonds[10] or C–OH bonds[11] has attracted considerable attention. Transition metal-catalyzed amine alkylation with alcohols has attracted much interest in recent years.[11,12] However, these methods are still subject to drawbacks such as the use of inaccessible and expensive homogeneous catalysts (*e.g.* Ru, Rh, Ir, *etc.*), restriction to aniline or benzylic/allylic alcohols, or require harsh conditions.[13,14] Very recently, Isobe and co-workers reported a Pd/C catalyzed one-pot reductive mono-alkylation of nitro aryls with hydrogen.[15a] Pinto and co-workers observed an unexpected one-pot azide reduction-*N*-dimethylation in methanol (or diethylation in ethanol) in the presence of Pd/C and under a hydrogen atmosphere at 70 psi.[15b] More recently, Ruano and co-workers reported the RANEY®-nickel-catalyzed mono-alkylation of primary amines and *N*-sulfinyl derivatives with alcohols at room temperature.[16] Nitriles have also been used as alkylating agents for *N*-alkylation.[15c,d]

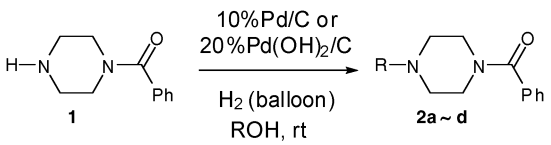
In connection with our interest in the development of simple and efficient methodology,[17] we report herein a mild and efficient Pd/C-catalyzed alkylation of amines/amino acids using alcohols as alkylating reagents.

In view of the broad spectrum of pharmacological activities possessed by piperazine-containing molecules,[18] and Pd/C or $Pd(OH)_2/C$ as easily available heterogeneous catalysts, piperazine derivative **1** was selected as the substrate, and the former as catalysts for our investigations. The *N*-alkylations of piperazines using different alcohols as the solvent, were investigated with either 10%Pd/C or 20%$Pd(OH)_2$/C as catalyst at room temperature. The results are summarized in Table 1. As can be seen from the Table, MeOH, EtOH, *n*-PrOH and *i*-PrOH can serve as the alkylating agents; both 10%Pd/C and 20%$Pd(OH)_2$/C can be used as the catalyst with the former being more effective. It might be due to the steric effect that the alkylation with *i*-PrOH required a longer time and the reaction was incomplete.

A survey of the literature revealed that Pd/C-catalyzed alkylation of amines with alcohols can occur without the use of hydrogen. However, the reactions need to be performed at 80–120 °C.[19] Our controlled experiments showed that at room temperature H_2 was necessary for the *N*-alkylation of an amine with an alcohol. A plausible mechanism is shown in the ESI†, which involves firstly the conversion of an alcohol into the corresponding aldehyde or ketone by Pd/C-catalyzed dehydration, followed by the consecutive imine formation and Pd/C-catalyzed hydrogenation to give the corresponding amine.[12b,20]

A shortcoming of the method is that the alcohol needs to be used as a solvent. To overcome this drawback, the recovery

Table 1 Alkylation of amine **1** with alcohols[a]



Entry	Amine	Alcohol (R^3OH)	T_1/T_2/h[b]	Product (R)	Y_1/Y_2 (%)[b]
1	**1**	MeOH	21/47	**2a** (Me)	85/62
2	**1**	EtOH	20/44	**2b** (Et)	89/74
3	**1**	*n*-PrOH	30/50	**2c** (*n*-Pr)	76/92
4	**1**	*i*-PrOH	138/ND[c]	**2d** (*i*-Pr)	64/ND[c]

[a] *Reaction conditions*: 0.1 mmol of amine in 5 mL of alcohol in the presence of 100 mg of 10%Pd/C or 80 mg of 20%$Pd(OH)_2$/C at rt. [b] T_1, Y_1 and T_2, Y_2 correspond to the reaction time and isolated yield using Pd/C or $Pd(OH)_2$/C as the catalyst, respectively. [c] ND = not determined.

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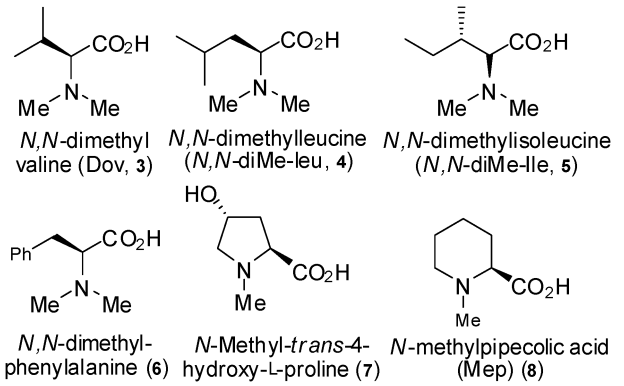


Fig. 1 Some *N*-methyl, and *N*,*N*-dimethyl-amino acid residues found in bioactive natural products.

and re-use of both the solvent and catalyst were investigated. The results showed that the catalyst can be easily recovered by a simple filtration and reused without a loss of activity after four cycles (*cf.* ESI†). Similarly, about 80% of the solvent (alcohol) can be recovered by distillation and recycled.

Encouraged by these results, we then proceeded to investigate the applicability of this method for the direct synthesis of *N*-methyl and *N*,*N*-dimethylamino acids.[2] *N*,*N*-Dimethylamino acids constitute a salient structural feature of cyclopeptide alkaloids, a class of bioactive natural products with more than 200 members.[2c,d] For example, *N*,*N*-dimethyl valine (Dov, **3**, Fig. 1) is found in dolastatin 10 and dolastatin 15, as well as their analogues TZT-1027 (auristatin PE), cemadotin (LU103793), and synthadotin (ILX651), which are in clinical trials as anticancer agents.[21a,b] This residue also exists in grassystatins A–C, which are potent cathepsin E inhibitors recently isolated from marine cyanobacteria;[21c] other *N*,*N*-dimethylamino acid residues such as **4**–**6** are found in cyclopeptide alkaloids.[2c,d,22] In addition, *N*-methyl-*trans*-4-hydroxy-L-proline (**7**) is a natural product;[23] *N*-methylpipecolic acid (Mep, **8**) is found in tubulysins, a family of nine natural products that are able to suppress the growth of cancer cells with inhibitory activity exceeding that of the anticancer drugs vinblastine, and Taxol, by 20- to 100-fold![24]

As can be seen from Table 2, with 10%Pd/C or 20%$Pd(OH)_2$/C as a catalyst, the methylation of both primary and secondary amino acids in methanol went smoothly and produced the corresponding *N*-methyl or *N*,*N*-dimethylamino acids in good to excellent yields (Table 2, entries 1–8).

Remarkably, *N*-methylation of amino alcohol and phenol acids can be achieved in excellent chemoselectivity to afford exclusively the *N*-methylated product in high yields (entries 2 and 8). Similarly, reactions in ethanol gave the corresponding *N*-ethylamino acids in good to excellent yields (entries 9–10). In this manner, natural products **3** to **6** were synthesized directly from the corresponding amino acid in high yield.

Next, we carried out the one-pot debenzylation-*N*-methylation of polyhydroxylated pyrrolidine derivative **21**. To our satisfaction, under the 10%Pd/C-catalyzed hydrogenolysis conditions in methanol, the reaction of compound **21** gave, in one-pot, the desired debenzylation-*N*-methylation product *N*-methyl-2,5-dideoxy-2,5-imino-D-mannitol (*N*-methyl-DMDP) **22**[25] in 89% yield (Scheme 1). DMDP[26,27] is a strong inhibitor of

Table 2 Alkylation of amino alcohol/amino acids with alcohols under catalytic hydrogenation conditions[a]

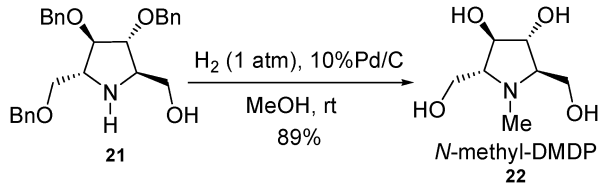
Entry	Starting material	Alcohol (R^3OH)	$T_1/T_2/h^b$	Product	Y_1/Y_2 (%)[b]
1	(*R*/*S*)-Pro (**9**)	MeOH	24/60	(*R*/*S*)-**10**	89/83
2	(2*S*,4*R*)-**11**	MeOH	48/ND[c]	(2*S*,4*R*)-**7**	87/ND
3	(*R*/*S*)-**12**	MeOH	27/59	(*R*/*S*)-Mep (**8**)	90/94
4	(*R*/*S*)-Leu (**13**)	MeOH	76/ND	(*R*/*S*)-**4**	94/ND
5	(*R*/*S*)-Phe (**14**)	MeOH	72/ND	(*R*/*S*)-**6**	92/ND
6	(*S*)-Val (**15**)	MeOH	80/ND	(*S*)-Dov (**3**)	93/ND
7	(2*S*,3*S*)-Ile (**16**)	MeOH	88/ND	(2*S*,3*S*)-*N*,*N*-diMe-Ile) (**5**)	91/ND
8	(*S*)-**17**	MeOH	29/ND	(*S*)-**18**	72/ND
9	(*R*/*S*)-Pro (**9**)	EtOH	26/44	(*R*/*S*)-**19**	85/75
10	(*R*/*S*)-**12**	EtOH	30/79	(*R*/*S*)-**20**	86/96

[a] *Reaction conditions*: 0.1 mmol of amine in 5 mL of alcohol in the presence of 100 mg of 10%Pd/C or 80 mg of 20%$Pd(OH)_2$/C at rt. [b] T_1, Y_1 and T_2, Y_2 correspond to the reaction time and isolated yield using Pd/C or $Pd(OH)_2$/C as the catalyst, respectively. [c] ND = not determined.

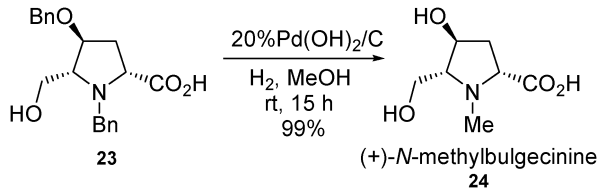
α- and β-glucosidases but shows weak inhibition against α-fucosidase.[26]

Interestingly, subjecting *N*,*O*-dibenzylbulgecinine **23** to 20%$Pd(OH)_2$/C or 10%Pd/C catalysts in methanol at room temperature, produced *N*-methylbulgecinine[27] **24** in almost quantitative yield (Scheme 2).

In summary, we have developed a mild (at rt, 1 atm H_2) heterogeneous Pd/C or $Pd(OH)_2$/C-catalyzed method for the monoalkylation of secondary amines and amino acids using



Scheme 1 One-pot debenzylation-*N*-methylation of pyrrolidine **21**.



Scheme 2 One-pot *O*-debenzylation-*N*-transalkylation of *N*,*O*-dibenzylbulgecinine **23**.

alcohols as alkylating agents. Using this method, naturally occurring amino acid residues **3** to **8** have been synthesized directly from the corresponding amino acid in high yields. Another feature of this method is the high efficiency in the one-pot debenzylation-*N*-methylation of polyhydroxylated pyrrolidine derivative **21**, and in the one-pot *O*-debenzylation-*N*-transalkylation of *N*-benzylamine **23**. Given that the benzyl group is the most widely used protecting group for amines and alcohols, and the *N*-methylated tertiary amine motif is present in many bioactive alkaloids and drugs, our method would find applications in the efficient synthesis of such amines.

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